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Stabilization of bimanual coordination due to active interhemispheric inhibition: a dynamical account

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Abstract. Based on recent brain-imaging data and congruent theoretical insights, a dynamical model is derived to account for the patterns of brain activity observed during stable performance of bimanual multifrequency patterns, as well as during behavioral instabilities in the form of phase transitions between such patterns. The model incorporates four dynamical processes, defined over both motor and premotor cortices, which are coupled through inhibitory and excitatory inter- and intrahemispheric connections. In particular, the model underscores the crucial role of interhemispheric inhibition in reducing the interference between disparate frequencies during stable performance, as well as the failure of this reduction during behavioral transitions. As an aside, the model also accounts for in- and antiphase preferences during isofrequency movements. The viability of the proposed model is illustrated by magnetoencephalographic signals that were recorded from an experienced subject performing a polyrhythmic tapping task that was designed to induce transitions between multifrequency patterns. Consistent with the model's dynamics, contra- and ipsilateral cortical areas of activation were frequency- and phase-locked, while their activation strength changed markedly in the vicinity of transitions in coordination.

1 Introduction

The neural underpinnings of bimanual coordination are still far from understood, but with recent advances in brain recording, pertinent data are accumulating rapidly. While early studies on monkeys revealed activations of various cortical areas, including the contralateral primary motor cortex (M1), premotor cortex (PM1), supplementary motor area (SMA), sensorimotor cortex, as well as interhemispheric cross-talk via the corpus callosum (Gazzaniga 1966; Mark and Sperry 1968; Brinkman and Kuypers 1972; Brinkman 1984; Tanji et al. 1988), more recent brain-imaging studies identified further contributions of the bilateral secondary somatosensory areas, the basal ganglia, the ipsilateral cerebellum (Deiber et al. 1991; Mima et al. 1999), and the primary sensorimotor cortex (Kawashima et al. 1994; Okuda et al. 1995). In spite of this development, however, the derivation of theoretical models providing an encompassing functional interpretation of such data remains a formidable challenge that will occupy neuroscientists for years to come. In this study, we seek to understand the possible functional role of bilateral activation patterns during bimanual coordination tasks, because sufficient pertinent neurophysiological data are available about this particular aspect of the neural processes underlying bimanual coordination to (attempt to) formulate a plausible interpretation.

First of all, there is ample evidence that both hemispheres are actively involved in the performance of one-handed movements. Baraldi et al. (1999) found support for the participation of two separate neural populations in each hemisphere, one in M1 and one in PM1: the first being activated during contralateral finger movements only, whereas the second exhibited signal changes during movements of either hand, indicating that unimanual movements are accompanied by cortical activity in both hemispheres. Compared to paced movements, self-paced rhythmic finger movements generally recruit more and larger neuronal populations that typically include (bilateral) SMA (Halsband et al. 1993; Freund 1996; Kaiser et al. 2000; Ohara et al. 2000) and (ipsilateral) PM1 (Stippich et al. 2000), especially during difficult tasks (Mayville et al. 2002). In addition, several research groups found unilateral cortical activation during discrete and (symmetrical) bihemispheric activation during sequential unimanual motor behaviors (Cheyne and Weinberg 1989; Pulvermüller et al. 1995; Manganotti et al. 1998; Andrew and Pfurtscheller 1999; Babiloni et al. 1999; Pfurtscheller et al. 2000), indicating the presence of an active (time-varying) cross-talk between bilateral and mesial central and prefrontal regions. On the basis of such findings, Gerloff et al. (1998) suggested that even simple voluntary movements cause exigencies prompting the motor system to

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respond by increasing not only the regional activation but also the information flow between hemispheres. In particular, links between bilateral motor areas may play an important role in suppressing mirror movements, that is, associated movements in arms or hands not intended to move (Armatas et al. 1994; Leinsinger et al. 1997; Gerloff et al. 1998; Daffertshofer et al. 1999), implying that those connections are effectively inhibitory. The existence of interhemispheric inhibition has indeed been demonstrated by applying transcranial magnetic (conditioning) stimuli over the motor cortex in one hemisphere, which turned out to affect responses to stimuli over the motor cortex in the other hemisphere (Ferbert et al. 1992; Meyer et al. 1995; Boroojerdi et al. 1996; Ikeda et al. 2000; Hanajima et al. 2001; Meyer-Lindenberg et al. 2002). The interhemispheric inhibition in question may be achieved directly via the corpus callosum, although various cortical areas may play a mediating role (for review see, e.g., Chen et al. 2003).

If one-handed movements are already accompanied by active inhibition of the contralateral hemisphere, then such inhibition will surely play a role in the performance of bimanual movements, especially when the hands oscillate at distinct frequencies, as in polyrhythmic tapping. During the performance of such multifrequency tasks, the interactions between the limbs are crucial as is illustrated by the fact that different frequency ratios vary considerably with regard to their difficulty of performance even though the unimanual sub-tasks are equally simple to execute (Summers et al. 1993; Peper et al. 1995a,b). The crucial role of the interactions is stressed further by the fact that spontaneous transitions between frequency ratios can be induced by gradually decreasing the overall cycle time of the pattern (Peper et al. 1995a,b), a phenomenon that has been modeled in terms of nonlinearly coupled self-sustaining oscillators (Haken et al. 1996). There are at least two reasons why such behavioral transitions in multifrequency coordination offer an expedient window into understanding the role of active interhemispheric inhibition in bimanual coordination.

First, during the performance of multifrequency tasks the two hands oscillate at separate frequencies, allowing for a discrimination of correlations between neural activity and movements of the left and right hand, respectively, through conventional spectral decomposition. According to an active interhemispheric inhibition hypothesis, the oscillatory frequencies of both hands should be present (and hence detectable) in both hemispheres. Furthermore, when a behavioral transition occurs from one frequency ratio to another, the frequency of at least one of the oscillating hands (probably the slow hand) is modified, which may be expected to result in a mismatch between the active interhemispheric inhibition and the actually performed frequency, and thus in an abrupt reconfiguration of the oscillatory frequencies that are present in the cortical activity of both hemispheres.

Second, within the vicinity of such transitions only a small number of relevant components suffice to characterize the system's properties: close to transition points the dimensionality of brain activity is drastically reduced, allowing for the construction of low-dimensional, dynamical models of brain functioning (e.g., Haken et al. 1996). Based on previous investigations of patterns of brain activity during the performance of unimanual and bimanual isofrequency tasks (Kelso et al. 1992; Wallenstein et al. 1995; Daffertshofer et al. 2000; Fuchs et al. 2000; Mayville et al. 2001) and corresponding modeling work (e.g., Frank et al. 2000; Jirsa et al. 2002), it may be expected that the spatiotemporal brain activity patterns during multifrequency tasks can be described in terms of a few dynamical processes and their couplings. These couplings, which are brought about via inhibitory and excitatory inter- and intrahemispheric connections, are of essential importance because they may invoke entrained (i.e., coherent) activity distributions, both within and across hemispheres, as well as spontaneous transitions between such distributions.

2 Modeling rhythmic movement

To formalize the crude, qualitative interpretation of the neural underpinnings of bimanual coordination forwarded in the preceding discussion, we build on earlier theoretical studies of spatiotemporal patterning in the brain (e.g., Winfree 1967; Wilson and Cowan 1972; Freeman 1975; Ermentrout and Cowan 1979; Nunez 1995; Jirsa and Haken 1996; Liley et al. 1999; Frank et al. 2000; Fuchs et al. 2000; Wright et al. 2001). Emanating from large ensembles of mutually interacting neurons, averaging methods like mean-field approaches result in weakly nonlinear mappings from action potentials to dendritic currents. Since the latter may be considered as generators of extracellular fields, ensemble or field-theoretical descriptions of the neocortex yield the macroscopic dynamics of distinct cortical areas as studied encephalographically – see, e.g., Frank et al. (2000) and Jirsa et al. (2002) for recent discussions and explicit derivations. To capture the main aspects of pertinent data, however, we here abstain from such ensemble or field-theoretical approaches but simply assume that pulse rates and/or dendritic currents have oscillatory properties. In other words, we ignore spatial features of the resulting brain waves and focus instead on temporal characteristics that are present in distinct yet coupled cortical areas.

In accordance with Fig. 1, we describe the macroscopic activity in M1 by complex-valued quantities R and L for the right and left hemisphere, respectively. The recorded activities are then given by $|R| = \sqrt{R^* R}$ and $|L| = \sqrt{L^* L}$, i.e., the modulus of R and L, respectively, where $(\cdots)^*$ refers to conjugate complex values. To deduce the dynamics of the relative phase between R and L in the context of rhythmic movements, these quantities are modeled in terms of self-sustaining oscillators that are frequency- and phase-locked due to their instantaneous coupling. Symmetry permits restricting calculations to one hemisphere, for example the right. For the self-sustaining component of the M1 dynamics of the right hemisphere (R) we posit the form $dR/dt - (\gamma_R - i\omega_R)\, R + |R|^2\, R$. The quantity ω_R represents the oscillator's frequency and γ_R a factor of a

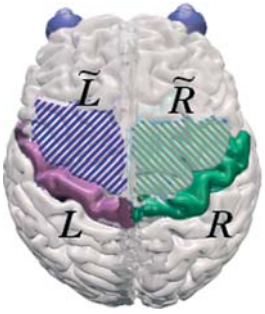

Fig. 1. Contributing cortical areas: M1 (R and L) and premotor areas ($\tilde{R}$ and $\tilde{L}$). The real-valued activities are given by the modulus of the indicated variables, e.g., $|R| = \sqrt{R^* R}$ or $|L| = \sqrt{L^* L}$

linear energy pump for the unit R whose amplitude saturates due to the cubic damping.[1] The dynamics of R is further affected by two factors: first, it is directly driven by the activity in M1 of the opposite hemisphere, L, and, second, an additional unit, here referred to as $\tilde{R}$, inhibits the cross-talk by mediating the L activity. For the sake of simplicity, we consider a linear coupling that can be formalized as $\left(\tilde{R}_0 - \tilde{R}\right)^* (L - L_0)$, where $\tilde{R}_0$ and L_0 denote coupling offsets; note that in the following we ignore any offsets so that the bilinear coupling is proportional to $\tilde{R}^* L$. Then, the total dynamics of R becomes

$$\frac{dR}{dt} - (\gamma_R - i\omega_R)\, R + |R|^2 R = \eta_{L\to R} L - \eta_{\tilde{R}\to R} \tilde{R}^* L\,, \qquad (1)$$

where $\eta_{L\to R}$ and $\eta_{\tilde{R}\to R}$ represent coupling strengths. The unit $\tilde{R}$, in turn, receives input from both motor areas L and R. In order to focus on the essential character of the (bi-)linear coupling, we consider $\tilde{R}$ to have minimal intrinsic properties that are captured by a linearly damped oscillatory system. We again ignore coupling offsets and neglect cross-coupling by means of $\eta_{\tilde{R}\leftarrow L} = 0$ so that the dynamics of $\tilde{R}$ reads

$$\frac{d\tilde{R}}{dt} + \left(\kappa_{\tilde{R}} + i\Delta\omega_{\tilde{R}}\right) \tilde{R} = \eta_{\tilde{R}\leftarrow R} L^* R\,. \qquad (2)$$

The four oscillatory units and their couplings that compose the dynamical system described by (1) and (2) are depicted in Fig. 2.

As will be shown in the following discussion, marked differences in the intrinsic time scales of the synchronization dynamics in M1s and premotor areas allow for a formal elimination of the evolution of the premotor activities. As a result, two nonlinearly coupled oscillators suffice to represent the combined dynamics if all four units (bilateral motor and premotor areas) are locked during stable performance. However, if one were to start with two units only, e.g., through an exclusive coupling between the two M1s, then one would not be able to describe both stable entrainment patterns and transitions between them. For instance, $\eta_{\tilde{R}\to R} = 0$ will result predominantly in mirror activity between hemispheres and deviations thereof

[1] Able that this form represents a nonlinear oscillator with solution

$$\frac{dR}{dt} - (\gamma_R - i\omega_R)\, R + |R|^2 R = 0 \Rightarrow R(t) = \pm\gamma_R^{\frac{1}{2}} \mathrm{e}^{-i\omega_R t}.$$

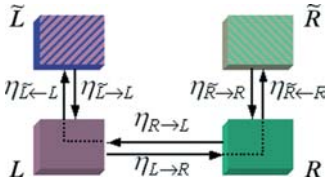

Fig. 2. Schematic representation of the connections between bilateral M1 (R and L) and premotor areas ($\tilde{R}$ and $\tilde{L}$); cf. (1) and (2), as well as Fig. 1. The macroscopic activity in both M1s is the product of self-sustained but frequency-/phase-locked oscillations at the corresponding movement frequencies. The M1s are coupled with each other through transcallosal connections (e.g., $\eta_{L\to R} L$). In addition, two bilateral premotor areas are coupled to both contralateral and ipsilateral M1s (e.g., $\eta_{\tilde{R}\leftarrow R} L^* R$) and respond (almost) instantaneously to their inputs. In turn, the activity of these additional units is (linearly) mapped onto the corresponding M1 (e.g., $\eta_{\tilde{R}\to R} \tilde{R}^* L$). Assuming that the connections between primary motor and premotor areas within a hemisphere are inhibitory (Daskalakis et al. 2002; Schneider et al. 2002; Stinear and Byblow 2003, 2004), an eventual loss of inhibition will cause an increased (residual) activity in (both) corresponding units

require additional (in)adequately phase-locked intrahemispheric inhibitory influences of premotor areas by means of, e.g., $\eta_{\tilde{R}\to R} > 0$. As will be discussed in detail, phase transitions between frequency and phase locks may be explained by a loss of effective inhibition within a hemisphere. On this account, changes in contra- and ipsilateral activity may reflect a loss of properly timed inhibition (for review see, e.g., Hamzei et al. 2002).

2.1 Stable rhythmic performance

In order to formalize the elimination of the premotor activities' dynamics and the so obtained reduction in dimensionality, we first transform $R = r\mathrm{e}^{-ip\Omega t}$ and $L = l\mathrm{e}^{-iq\Omega t}$. Notice that the oscillatory components of the M1 and premotor dynamics as such are not of central interest, although this transform readily implies that R and L oscillate with a fixed ratio $p:q$, given an externally prescribed common frequency Ω. For stable performance of a $p:q$ polyrhythm, we additionally employ $\Delta\omega_{\tilde{R}} = (p-q)\,\Omega$, yielding $\tilde{R} = \tilde{r}\mathrm{e}^{-i\Delta\omega_{\tilde{R}} t} = \tilde{r}\mathrm{e}^{i(q-p)\Omega t}$. As a consequence, the dynamics (2) can be rewritten via complex-valued amplitudes as $d\tilde{r}/dt + \kappa_{\tilde{R}}\tilde{r} = \eta_{\tilde{R}\leftarrow R} l^* r$. Because $\tilde{R}$ is driven by both L and R and inhibits the cross-talk $L \to R$, we suppose that its characteristic time is sufficiently small. That is, $\tilde{R}$ is frequency- and phase-locked with L and R. Notice that if we do not presume such locking with respect to, for instance, the left unit L, then $\tilde{R}$ will oscillate additionally with frequency ω_L. Expressed in more general terms, $\tilde{R}$ instantaneously follows the dynamics of R and L because the time scale of $\tilde{r}$ is small compared to the time scales of r and l and the time scales prescribed by the oscillations ω_R and ω_L; importantly, this assumption does not imply that the generating neural processes evolve at different time scales but rather that the corresponding neural clusters have synchronization dynamics that are poles apart. Under those circumstances, $\tilde{r}$ basically acts as (amplitude) filter and, accordingly, we can eliminate its dynamics adiabatically by means of $d\tilde{r}/dt \approx 0$, yielding

$$\frac{d\tilde{r}}{dt} + \kappa_{\tilde{R}}\tilde{r} = \eta_{\tilde{R}\leftarrow R} l^* r \xrightarrow[\text{elimination}]{\text{adiabatic}} \tilde{r} \approx \frac{\eta_{\tilde{R}\leftarrow R}}{\kappa_{\tilde{R}}} l^* r\,. \qquad (3)$$

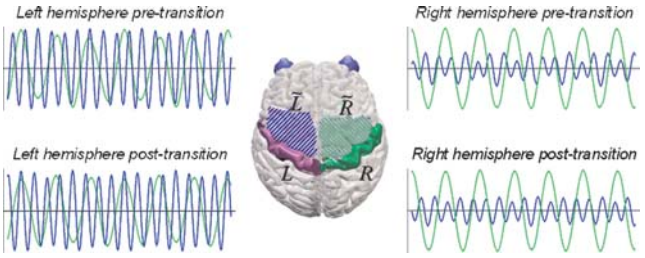

Fig. 3. Distributions of participating cortical areas (*middle panel*) – see also Fig. 1: bilateral M1 (R and L) and premotor areas ($\tilde{R}$ and $\tilde{L}$). Next to every unit the time-dependent activities are depicted that were obtained by simulating (1) and (2); *upper rows* 3:8 frequency locking – pretransition, *lower rows* 1:3 frequency locking – posttransition. The *left panels* show the evolution of the real parts of L (*blue*) and $\tilde{L}$ (*green*), and the *right panels* depict R (*green*) and $\tilde{R}$ (*blue*). The transition is realized by a reduction of the oscillators via a drop in $\gamma_{R,L}$; *upper panels* $\gamma_{R,L} = 0.5$; *lower panels* $\gamma_{R,L} = 0.1$; remaining parameters: $\omega_R = 1, \omega_L = 3/8, \kappa_R = \kappa_L = 0.5, \Delta\omega_{\tilde{R}} = \omega_R - \omega_L = -\Delta\omega_{\tilde{L}}$, $\eta_{L\to R} = \eta_{R\to L} = 0.01, \eta_{\tilde{R}\to R} = \eta_{\tilde{L}\to L} = 0.1, \eta_{\tilde{R}\leftarrow R} = \eta_{\tilde{L}\leftarrow L} = 0.25$. Note that in (2) an offset was used to allow for oscillations in $\tilde{R}$ and $\tilde{L}$ (offset value = 1)

When substituting this form into (1) and accounting for the aforementioned transformations, the amplitude dynamics in the right M1 reads

$$\frac{dr}{dt} - \gamma_R r + |r|^2 r \approx \left(\eta_{L\to R} l - \frac{\eta^*_{\tilde{R}\leftarrow R}\eta_{\tilde{R}\to R}}{\kappa_{\tilde{R}}} l^2 r^*\right) \mathrm{e}^{i(p-q)\Omega t}. \quad (4)$$

Since r and l are still complex quantities, we recast them in terms of real-valued amplitudes and phases, $r = \rho \mathrm{e}^{i\varphi_R}$ and $l = \lambda \mathrm{e}^{i\varphi_L}$, and obtain for the phase:

$$\frac{d\varphi_R}{dt} = \eta_{L\to R}\frac{\lambda}{\rho}\sin\left[\varphi_L - \varphi_R + (p-q)\,\Omega t\right] - \frac{\eta^*_{\tilde{R}\leftarrow R}\eta_{\tilde{R}\to R}}{\kappa_{\tilde{R}}}\lambda^2 \sin\left[2\,(\varphi_L - \varphi_R) + (p-q)\,\Omega t\right]. \quad (5)$$

This dynamics covers the phase evolution during stable multifrequency performance provided that left and right M1s are $p:q$ frequency-locked (Daffertshofer et al. 2000).

2.2 Special case: isofrequency movements

As an aside, we briefly consider the dynamics (5) for cases of bimanual performance in which the oscillators have identical frequencies. In fact, the $p:q = 1:1$ coordination mode can be considered stable in terms of frequency locking, but what about the corresponding phase locking? If ω_R and ω_L are equal, or, equivalently, if $p = q$, the dynamics (5) yields the following equation[2] for the dynamics of the relative phase $\phi = \varphi_R - \varphi_L$ between R and L:

$$\frac{d\phi}{dt} = -A\sin\phi - B\sin 2\phi\,.$$

This simple structure represents a well-established dynamics of rhythmic isofrequency interlimb coordination that describes switches in coordination from anti- to inphase patterns (i.e., from mirrored to synchronous movements) with increasing movement frequency (Haken et al. 1985; Beek et al. 2002; Swinnen 2002). Complementing the results of phenomenological, behavioral studies, our modeling results suggest that an increase in frequency may affect (i) the amplitudes of activity in the two M1s, (ii) the strength of activity in premotor areas, and/or (iii) the degree of phase locking between the M1s and premotor areas, and may therefore induce behavioral changes.

2.3 Phase transitions between frequency and phase locks

The identified dynamics not only has interesting implications for isofrequency coordination. In general, a change in movement frequency may change the amplitudes of the contributing oscillators [see (4)]. Due to such amplitude changes (or changes in activation strength), a dynamics like (5) may show phase transitions, i.e., abrupt switches between different frequency and phase locks (Haken et al. 1996), as is illustrated in Fig. 3.

In Fig. 3 we chose to depict frequency locks that match the encephalographic recordings that will be discussed in the next section illustrating the viability of the proposed model. We obtained Fig. 3 by simulating the dynamics (1) and (2) such that an abrupt shift occurred from the initial 3:8 mode lock to a final 1:3 mode lock. This shift was induced by decreasing the linear parameters $\gamma_{R,L}$ resulting in a drop in amplitude [see (1) and Fig. 3].

To anticipate, the data to be discussed in the next section exhibited several features that are fully consistent with the dynamics of the derived model. While distinct contra- and ipsilateral cortical areas of activation were frequency- and phase-locked to the movements, their activation strength changed markedly in the vicinity of phase transitions between frequency ratios: we found strong residual activity in the ipsilateral hemisphere locked to the left (adapting) finger during phase transitions. Interpreted in terms of the presented model, these changes in activity strengths can be explained by decreasing differences in time scales between M1 and premotor areas caused by increasing movement frequency. Recall that the stable entrainment dynamics was derived through adiabatic elimination of the premotor-related variable $\tilde{r}$ [see (3)], which implies that premotor activities are instantaneously phase-locked to the oscillatory activities in both M1s. On this account, the loss of phase locking may be understood as a reflection of the adiabatic elimination becoming inappropriate[3] so that $\tilde{r}$ no longer acts as a passive (filter) unit. Recall further that the premotor areas served as inhibitory processes [see (1)], implying that an inadequate phase locking coincides with a loss of inhibition. Put differently, according to our model, the sum of left/right couplings is "negative" (antiphase). Thus, the effective interhemispheric coupling is inhibitory. A loss of this inhibition goes along with inadequate phase locking and with a switch in behavior.

[2] We abbreviate $A = \left[\eta_{L\to R}\lambda^2 - \eta_{R\to L}\rho^2\right]/\lambda\rho$ and $B = \eta^*_{\tilde{L}\leftarrow L}\eta_{\tilde{L}\to L}\rho^2/\kappa_{\tilde{L}} - \eta^*_{\tilde{R}\leftarrow R}\eta_{\tilde{R}\to R}\lambda^2/\kappa_{\tilde{R}}$.

[3] An increasing tempo may lead to the case where the time scales of phase adaptation and (basic) oscillatory activities do not sufficiently differ, i.e., the adiabatic elimination has become invalid.

3 Cortical activity during rhythmic movement

3.1 Methods

Brain activity was recorded using a 151-channel whole-cortex MEG system (CTF Systems Inc., Vancouver, Canada). The sensors were distributed uniformly over the helmet surface with a mean spacing of 3.1 cm. The superconducting quantum-interference devices were first-order axial hardware gradiometers with 2-cm coil diameter and 5-cm baseline. An array of 29 reference sensors (magnetometers and gradiometers) was used for noise cancellation by means of third-order synthetic gradiometers (total noise level was less than 10 fT rms/$\mathrm{Hz}^{1/2}$). Head position was established using coils located at the nasion and left and right preauricular points. Data were acquired at a sampling rate of 312.5 Hz with a bandwidth from DC to 100 Hz after online filtering using a fourth-order Butterworth low-pass filter at 100 Hz and notch filters at $k \times 50$ Hz. In all experimental trials a subject (a right-handed male drummer, 35 years of age, who had signed an informed consent) was seated in a comfortable position (head in helmet, eyes closed, lower arms/hands resting on the armrests while tapping with his index fingers). The subject was instructed to synchronize the right finger taps to acoustic stimuli (faster cadence) that were presented to the right ear (tone duration 40 ms, pitch 400 Hz; EARTone 3A Insert Earphones, Cabot Safety Corporation) and, at the same time, to tap with the left finger in a polyrhythmic ratio of 3:8 or 5:8 to the right taps (slower cadence). The acoustic signal was used to define 17 tempo plateaus. The first plateau lasted for nine rhythmical cycles (i.e., 9×8 acoustic stimuli at the right ear, pacing frequency 2.5 Hz), and during the first six cycles an additional acoustic signal was also presented to the left ear (tone duration 40 ms, pitch 200 Hz) in order to prescribe the desired polyrhythm (pacing frequency 0.94 Hz [1.56 Hz] for the 3:8 [5:8] polyrhythm). The remaining plateaus each involved three rhythmical cycles, and the tempo of stimulus presentation increased over the consecutive plateaus from 2.5 Hz to about 6.7 Hz in steps of -6% of the interstimulus period for the right ear, resulting in a trial duration of approximately 2 min. For both polyrhythms 72 trials were conducted (total: $2 \times 72 = 144$ trials) in blocks of 12 identical trials presented in alternating order divided over three sessions on different days. The subject was instructed to keep up with increases in tempo by means of synchronizing the right finger taps with the uniaural stimuli and adjusting the tempo of the left finger taps in accordance with the initial polyrhythm. Eventual spontaneous changes in coordination, however, were not to be resisted. Taps of both index fingers were monitored using optical switches (mounted on the armrest; button height: 2 mm; trigger height: 1.5 mm above surface of armrest) and sampled simultaneously with the MEG. The experiment was approved by the scientific committee of the MEG center of the Royal Netherlands Academy of Arts and Sciences (KNAW) before it was conducted, under a general approval for this type of MEG experiment by the ethical committee of the Vrije Universiteit Medical Center.

Data processing. To avoid potential errors due to signal-size-dependent filter effects (Press et al. 2002), we rescaled time such that the intertone intervals, that is, the tempo of the auditory stimulation at the right ear, were constant across plateaus (up-sampling via cubic spline interpolation leading to equal signal lengths of $(3 \times 8/2.5) \times 312.5 = 3000$ samples per plateau). The data were further high-pass filtered, eliminating possible low-frequency drifts (bidirectional fourth-order Butterworth filter, cutoff frequency 0.15 Hz). For the two tapping signals (optical switch data) we estimated the per-plateau power spectral density using Welch's periodogram method providing a frequency resolution of $\Delta f = 3.5 \times 10^{-2}$ Hz (see Matlab 6.5, Mathworks, Natick, MA). We subsequently determined the actual frequency-locked ratio between the movements of the two fingers by establishing a rescaling of the frequency axis of the left finger's periodogram that maximized the overlap between the two spectra. Based on the ensuing rational scaling factors, which reflected transitions like 3:8 $\rightarrow$ 1:3, we combined trials that contained initial switches in frequency locking at the same tempo (typically between 4.5 and 5.5 Hz) by averaging the corresponding encephalographic signals. For these mean trials (six in total, each associated with a particular transition frequency) we analogously estimated the power spectral densities after rescaling each time series to unit variance. Finally, we depicted the spectral power at both the left and the right fingers' movement frequency over the scalp by means of conventional interpolated Mercator maps.

3.2 Results

Decomposition of magnetoencephalographic (MEG) signals into spatial and temporal components as well as cross-spectral analyses revealed different spatial correlations within different frequency regimes. As in previous studies (Lang et al. 1990; Daffertshofer et al. 2000; Gerloff and Andres 2002), bimanual tapping was accompanied by frequency- and phase-locked activations of the motor cortices in both hemispheres. Various cortical areas appeared to be linearly correlated as they showed oscillatory activity at the two (unimanual) movement frequencies, suggesting that bimanual patterns could be expressed as superposition of unimanual ones. The activation patterns, however, changed radically when behavior became unstable. Starting with a frequency ratio of 3:8 or 5:8, an increase in overall tempo led to cascades of transitions to ratios consisting of small integers, e.g., 3:8 $\rightarrow$ 1:3 $\rightarrow$ 1:2 $\rightarrow$ 1:1. The motor output showed that the paced right (fast) finger was always 1:1 frequency-locked with the acoustic stimulation, whereas changes in tempo of the left (slow) finger gave rise to the aforementioned changes in frequency locking. Accordingly, the spatial distributions of the spectral power associated with the fast (right) limb roughly remained unaltered irrespective of the increasing tempo and reflected a dominant activity at the contralateral (left) hemisphere. Before and after a phase transition the spectral power at the frequency of the slow (left) finger had equivalent (mirrored) spatial distributions, again

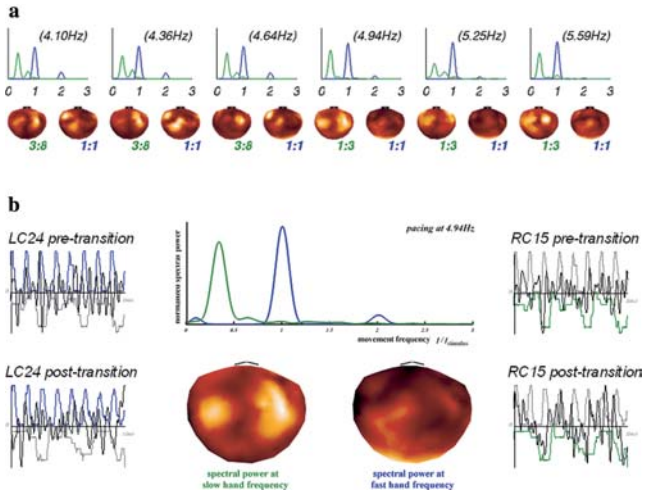

Fig. 4. a Example of the changing spatial distributions of spectral power of MEG signals during spontaneous transitions in multifrequency tapping. *Line graphs*: Power spectral densities over normalized frequencies of the left (*green*) and right (*blue*) finger tapping at subsequent tempi (*columns*). *Colored maps*: Normalized spectral power of the MEG signals at the frequency of both the left, slow finger (to the *left* of each *panel*) and the fast, right finger (to the *right* of each *panel*) by means of spatial two-dimensional maps (interpolated between sensor locations, nasion at *top*) ranging from small (0 = *black* followed by *dark red*) to large values (*yellow* followed by *white* = 1). The ratios reflect the frequency locks to the pacing signal. A change from a 3:8 to a 1:3 coordination mode occurs around 4.94 Hz (frequency of the fast, right hand) and is associated with increasing ipsilateral activity at the frequency of the slow hand (*fourth column, left panel*). **b** The *middle panels* show the spatial distribution of the spectral power at the two movement frequencies (*lower row*) and the corresponding power spectra of the motor output (*upper row*) – cf. Fig. 4a. The *black lines* in all the other *panels* display time series of MEG channels located above motor areas (*left panels* – left hemisphere, LC24; *right panels* – right hemisphere, RC15) prior to and around the switch in behavior (*upper* and *lower panels*, respectively); here, MEG data were filtered to improve the illustrations (fourth-order Butterworth band-pass filter between 1.3 and 20 Hz). Clearly, the high frequency that relates to the fast hand movement is reduced when comparing the transition regime with the stable performance (*left panels*, *black lines*). The remaining curves show the (*unfiltered*) motor output to indicate the relation between MEG and behavior [*blue*: right hand; *green*: left hand; *gray lines*: contralateral hand(s)]; note that the low-frequency components in the left (ipsilateral) hemisphere is in antiphase to the one in the right (contralateral) hemisphere

indicating a dominance of neural activity at contralateral motor areas. In contrast, in the immediate vicinity of switches in coordination the slow frequency component changed drastically by means of a strong increase of (relative) spectral power in the ipsilateral motor areas as depicted in Figs. 4a, b.

Since changes in neural activity were associated predominantly with the slow finger, which actually underwent the behavioral switches (relative to the pacing), the corresponding cortical areas may be assumed to participate in the transition. Put differently, these data revealed frequency locking with the movement frequency of the contralateral hand and, in the vicinity of a transition, frequency locking with the left (slow) hand in the ipsilateral hemisphere.

4 Discussion

We presented a dynamical model that was developed to account for the patterns of brain activity accompanying stable performance of bimanual multifrequency tasks, as well as behavioral instabilities in the form of phase transitions between frequency- and phase-locked patterns. The model implements a particular interpretation of recent findings regarding the neural processes underlying one-handed movements and bimanual coordination. The implemented interpretation underscores the crucial role of interhemispheric inhibition in reducing the interference between disparate frequencies during stable performance, as well as the failure of this reduction during behavioral transitions. Encephalographic data were discussed to illustrate the model's viability in accounting for the patterns of cortical activity accompanying the bimanual performance of multifrequency tasks. The implications of the model, however, are not restricted to this specific instance of rhythmic motor behavior. On the contrary, the proposed coupling mechanisms might be active during the performance of all kinds of bimanual and even unimanual tasks. In particular, the proposed coupling has at least three general characteristics: (i) the coupling is permanent because it is based on an instantaneous cross-talk between motor areas; (ii) the cross-talk is effectively inhibitory; and (iii) the strength and timing of the inhibition is continuously modified so as to meet environmental and task demands.

PM1 and/or SMA is known to be involved in the timing of coordinated movements, and they may well mediate interhemispheric connections, even though it has been suggested that M1 itself is not simply a passive unit (Donchin et al. 1998; Gerloff et al. 1998; Carpenter et al. 1999; Donchin et al. 1999; Cardoso de Oliveira et al. 2001; Gribova et al. 2002). This implies that M1 and PM1/SMA must be phase-locked for performance to be stable. In contrast, improper phase locking may result in behavioral instabilities. According to our model, phase transitions during multifrequency performance coincide with an insufficient and poorly timed inhibition. Note that for rhythmic behavior, inhibition can be interpreted as antiphase coupling between two units (M1 vs. PM1/SMA). As a result, the spectral power at the movement frequency in the corresponding motor areas may vanish because two superimposed antiphase-locked oscillations may cancel each other out. Deviations from such antiphase locking yield a finite amount of spectral power, as complete cancellation is no longer feasible. Our exemplar data showed a significant increase of activity ipsilateral to the finger undergoing the instability. This finding indicates that during changes in movement coordination the ipsilateral motor areas are less, or no longer, phase-locked and that, hence, the interhemispheric cross-talk is insufficiently suppressed. It seems likely that these effects are caused by interhemispheric inputs through the corpus callosum (cf. Introduction). The inhibitory influences of M1 on the activation of the ipsilateral hand, however, may to a significant extent be relayed (i.e., timed) below the cortex. This relay probably includes multiple (active) levels along

the neuroaxis-like ipsilateral oligosynaptic pathways and corticoreticulo- or corticopropriospinal projections (Ziemann et al. 1999; Leocani et al. 2000). Irrespective of the exact location of the postulated inhibitory mechanisms, the proposed model indicates that an eventual loss of inhibition may result in instabilities and phase transitions or, more generally, unintended motor output (Armatas et al. 1994; Leinsinger et al. 1997; Gerloff et al. 1998; Daffertshofer et al. 1999).[4]

Against this background, modeling neural cross-talk and ipsilateral control mechanisms during manual performance requires two M1s and additional cortical mediators; here the latter were summarized as premotor areas. Both M1s and the premotor areas synchronize, but the time scales on which synchronization is realized may differ. In that case, linear intra- and interhemispheric interactions can readily result in relative phase dynamics of cortical activity that reflect macroscopic properties of the respective movements. The present model for cortical activity during multifrequency bimanual movement was developed along these lines. Its brief application to isofrequency movements revealed that the relative phase between the two hemispheres obeys a well-established model that accounts for various stability properties of bimanual coordination. In this regard, the proposed model is not only consistent with previous studies on rhythmic coordination in unskilled subjects (e.g., Kelso et al. 1992; Wallenstein et al. 1995; Daffertshofer et al. 2000; Fuchs et al. 2000; Mayville et al. 2001) but also positions these studies in a broader theoretical framework, even though, as it stands, its explicit empirical test is limited to data from a single subject.[5] In contrast to those previous, more phenomenological studies, the model directly accounts for the existence of preferences for in- and antiphase coordination modes, which can be associated with the dominance of either interhemispheric excitation or intrahemispheric inhibition. Moreover, the model indicates that frequency-induced transitions between coordination modes are related to inadequate intrahemispheric phase locking.

In addition to the various studies summarized in the introduction, the theoretical interpretation presented here receives support from recent studies involving transcranial stimulation during rhythmic bimanual performances. For instance, Stinear and Byblow (2002) showed that intracortical inhibition is suppressed more when moving in synchrony than when moving asynchronously. Furthermore, inhibition seems to be metabolically less demanding than excitation due to large differences in the efficiency and number of corresponding synapses (Waldvogel et al. 2000). Although inhibition is therefore difficult to detect by, e.g., functional imaging, this lower energy demand motivates our interpretation of inhibitory processes as relaying mediators of interhemispheric couplings. Interestingly, by recording relative changes in averaged flow velocities in both middle cerebral arteries with transtemporal Doppler sonography, Cuadrado et al. (1999) showed that the contralateral activity due to unimanual movements is greater than that associated with bimanual movements, which suggests that inhibitory processes are active in the latter case.

In closing we submit that, in general, unimanual movements entail bilateral M1 activity, which is consistent with various recent findings (see Introduction). Because the contralateral M1 is far more active than its ipsilateral counterpart, it can, under normal circumstances, be considered the main controller of hand and finger movements (Gazzaniga 1966; Brinkman and Kuypers 1972). However, our theoretical and empirical results suggest that both M1s are significantly event related in terms of phase locking or, in the case of rhythmic movements, by means of frequency locking. Such bilateral activity patterns imply the presence of an instantaneous interhemispheric cross-talk between motor areas. The motor control system has to account for this interhemispheric information flow, and, especially when moving unimanually, the resulting ipsilateral activation should be reduced. In other words, during unimanual movements one of the two end-effectors needs to be actively suppressed by inhibiting its contralateral M1. Hence, starting with bimanual movements as the fundamental coordination mode, unimanual movements are realized by inhibiting ipsilateral motor areas, that is, by suppressing movement of the contralateral limb.

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[4] If inhibition is hampered, such as after a unilateral cerebral stroke, the unaffected M1 ipsilateral to the paralytic limb may take over functions from the damaged one (Chollet et al. 1991). This mechanism also seems responsible for the timing of bimanual movements when the transcallosal cross-talk is entirely absent (Geschwind and Kaplan 1998).

[5] As previously noted for this subject, the obtained characteristics proved to be rather robust. The transitions at the behavioral level were consistent with those in previous experiments involving multiple subjects (e.g., Peper et al. 1995a,b), and the MEG activity was similar for the six mean trials for the subject being studied. As such, the current data set provided an adequate starting point for future experimental tests of the model.

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